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Learning and Memory Enhancement by Neuropeptides
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As detailed in previous reports, the major purpose of this work, is to study biochemical mechanisms responsible for the toxic effects of the organometal neurotoxin trimethyltin (TMT) on learning, in order to develop strategies for prevention or alleviation of toxicity. Trialalkyltins are used as stabilizers for plastics, or as biocides for control of fungus, barnacles, bacteria and insects. These compounds are anti-fouling toxicants of specific interest to the Navy, because of potential of estuarine contamination from naval vessels, and as a danger to seamen on ships carrying paint containing these compounds, since desalinated water used on these vessels may become contaminated. These compounds are also of interest as a model treatments for study of learning/memory dysfunction resulting from exposure to other toxicants (e.g. other heavy metals, organic solvents), or arising from disease states. We study learning in an autoshaping task, in which rats learn to touch a lever to obtain food. During the 6 months, three papers have been published:

2 keywords: Toxicity; antifouling coatings; (N7)

Gerbec, E.N., Messing, R.B. and Sparber, S.B. Parallel changes in operant behavioral adaptation and hippocampal corticosterone binding in rats treated with trimethyltin. Brain Research 460 (1988) 346-351.

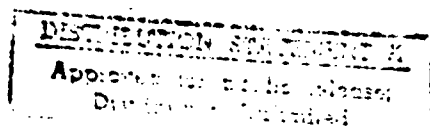
Messing, R.B., Bollweg, G., Chen, Q. and Sparber, S.B. Dose-specific effects of trimethyltin poisoning on learning and hippocampal corticosterone binding. Neurotoxicology 9 (1988) 491-502.

Messing, R.B., Allen, S.J., Aanonsen, L. and Sparber, S.B. Naloxone administration impairs autoshaped learning. Behavioral and Neural Biology 51 (1989) 34-45.

Also being prepared for publication is a study showing that rats treated with TMT or a mixed ganglioside preparation (which was administered to determine a possible therapeutic effect in TMT-treated animals) have decreased concentrations of hippocampal glucocorticoid receptors, which may be related to cognitive impairments. Interestingly, TMT-treated rats have elevated levels of glial fibrillary acidic protein (GFAP), an indication of the cytotoxicity produced by this compound. Rats treated with gangliosides, which induce a cognitive impairment but no cell death, have normal levels of GFAP, but still exhibit the decrease in corticosteroid binding. Thus, this decrease is probably independent of hippocampal cell death, and may be a down regulation. In future work we wish to examine the effects of manipulations of the pituitary-adrenal axis on TMT toxicity as measured behaviorally, biochemically and histologically.

Another manuscript currently being prepared concerns work showing that autoshaping is highly dependent upon the deprivation state of the animal: more food deprived rats learn faster. This is not simply a generalized behavioral activation produced by food deprivation, since more food deprived rats also show better learning of latent

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inhibition. It appears that deprivation state also influences the performance of rats exposed to TMT, similarly to its effect in normal animals. This is consistent with the capacity for a vasopressin analog to attenuate the learning deficit in rats treated with TMT, and indicates that the learning impairment is not absolute, but rather may be amenable to various palliative treatments. Our present research plans include studies investigating interactions between deprivation levels and effects of drugs and toxicants. Presently underway, is a study of interactions of food deprivation level and a vasopressin antagonist peptide, in normal rats and in rats treated with TMT.

Other work in progress includes the following:

1. We are investigating the neurotoxic effects of tributyltin, a compound that is commonly found in fungicides and anti-fouling agents. This compound is commonly thought of as an immune system toxicant in mammals; however, preliminary data indicate that it may affect brain corticosterone receptors.
2. Previous work [Messing and Sparber, Tox. Lett. 32 (1986) 107-112] showed an upregulation of forebrain β -adrenergic receptors in rats treated with TMT. This led us to hypothesize that forebrain norepinephrine release may be impaired in rats treated with TMT, and that this may be associated with behavioral deficits. Accordingly, Dr. Susan Sara, of the C.N.R.S., Gif-sur-Yvette, France, and myself investigated a possible difference in response to clonidine, a drug which attenuates forebrain norepinephrine release. We reasoned that the behavioral suppressant effect of this drug might be attenuated in rats given TMT, if indeed forebrain NE release was already deficient. This, in fact appears to be the case. We are currently investigating a possible difference in the inhibitory response of single cells in locus coeruleus to i.v. clonidine in rats given water or TMT.
3. Also, with Dr. Sara, we completed a study comparing TMT-treated and normal rats in the radial arm maze (RAM). Rats treated with a moderate (6.0 mg/kg) dose of TMT were not deficient in performing in the maze under "standard" conditions. However, if a 4 hr delay was imposed between entries into the fourth and fifth arms of the 8 arm maze, a memory deficit was apparent. The normal performance of the animals under standard conditions indicates that the memory deficit is not due to motivational or sensorimotor effects. Current work is correlating this deficit with size of the brain lesion produced by TMT.

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